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Enantioselective Total Synthesis of FR900482

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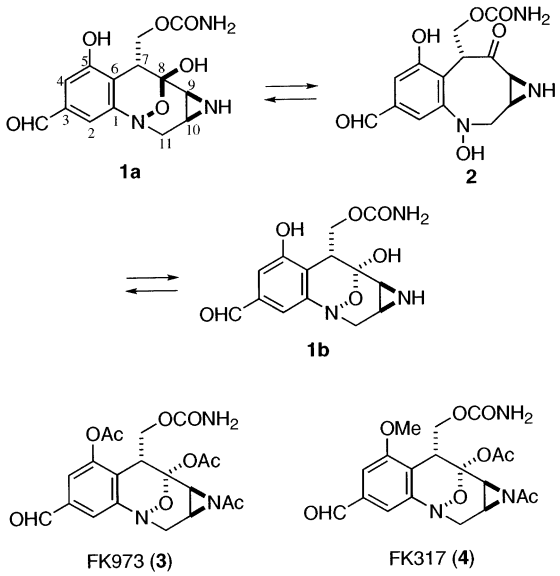
The development of two approaches for the enantioselective total synthesis of FR900482 is described. A precursor for the formation of the benzazocine ring was assembled effectively by a modification of the Sonogashira coupling of an aryl triflate with a chiral acetylene unit derived from tartaric acid and the subsequent novel ketone formation via conjugate addition of pyrrolidine to the *o*-nitrophenylacetylene derivative. The first-generation approach to the key pentacyclic intermediate of our racemic total synthesis utilizes an intramolecular Mitsunobu reaction of an *ω*-hydroxynitrobenzenesulfonamide to form the benzazocine ring and a stepwise sequence to construct the hydroxymethyl group at the C(7) position. The key intermediate could be synthesized in optically pure form via formation of the characteristic hydroxylamine hemiacetal and a stereoselective epoxide formation. In the second-generation approach, the *N*-hydroxybenzazocine ring could be constructed directly from an *ω*-formylnitrobenzene derivative by intramolecular reductive hydroxylamination. The crucial stereoselective hydroxymethylation and the formation of the hydroxylamine hemiacetal could be performed efficiently by a one-pot sequence. After leading to the pentacyclic key intermediate, the total synthesis of (+)-FR900482 was accomplished by a modification of our protocol established in the racemic total synthesis. Stereochemical issues involved in the hydroxymethylation at the C(7) position and formation of the hydroxylamine hemiacetal are also discussed in detail.

Introduction

FR900482 (**1**), existing as an equilibrium mixture of two tautomeric stereoisomers (**1a** and **1b**) and *N*-hydroxybenzazocinone (**2**), was isolated from the fermentation harvest of *Streptomyces sandaensis* No. 6897 at the Fujisawa Pharmaceutical Co. (Scheme 1).[1] This compound possesses potent antitumor activity against a number of tumor cell lines, including mitomycin C- and vincristine-resistant P388 leukemia cells.[2] In extensive efforts to develop more potent and less toxic agents, FK973 (**3**)[3] and FK317 (**4**),[4] semisynthetic derivatives from **1**, were found to be promising clinical candidates. The mode of action of this class of compounds has recently been proven through detailed mechanistic studies.[5] FR900482 (**1**) is activated by a two-electron reduction of the N−O bond to afford the benzazocinone derivative (**5**), which then cyclizes to give the mitosene species (**6**) (Scheme 2). Due to its high electrophilicity, this species covalently cross-links duplex DNA in the minor groove[6] and also DNA and oncoproteins, such as HMG I/Y protein.[7]

SCHEME 1. FR900482 (1) and Derivatives



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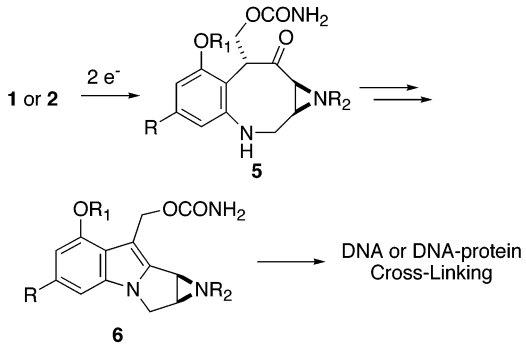
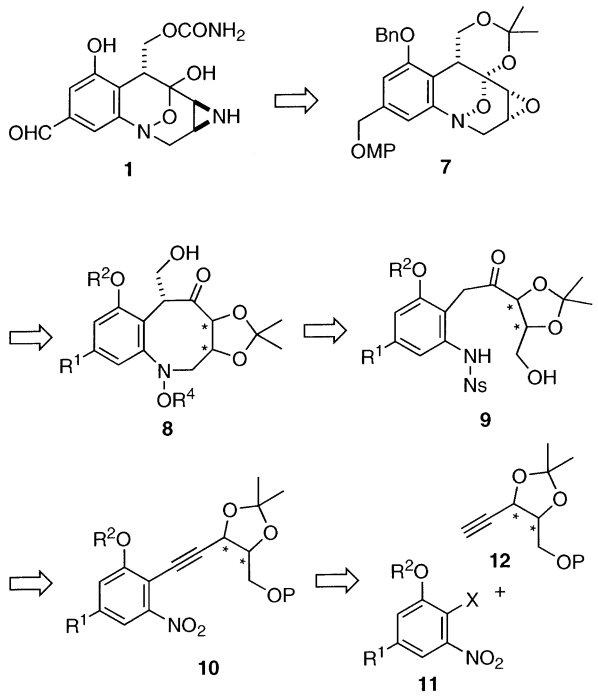
SCHEME 2. Proposed Mechanism of Action of FR900482 (1)



In addition to its highly potent activity, FR900482 (**1**) possesses unique structural features, including hydroxylamine hemiacetal, aziridine, and carbamoyloxymethyl groups, making it an attractive target for synthetic organic chemists. To date, numerous approaches[8] have been explored to construct this densely functionalized structure, and five total syntheses,[9−13] as well as two formal total syntheses,[14,15] have been reported. Our continuing efforts in this area have led to the first total synthesis of racemic FR900482 (**1**)[9] and a synthetic approach through development of [3 + 2] cycloaddition strategy.[16] We finally accomplished an enantioselective total synthesis of FR900482 (**1**) in optically pure form.[17] In this paper, we provide a full account of the development of the enantioselective total synthesis of FR900482 (**1**).

SCHEME 3. Retrosynthetic Analysis of FR900482 (1)



Results and Discussion

1. Synthetic Strategy. FR900482 (**1**) could be derived from the epoxide **7** using the synthetic route we established in the racemic total synthesis of **1** (Scheme 3).[9] Given the equilibrium between the diastereomeric hydroxylamine hemiacetals proceeding via the *N*-hydroxybenzazocinone (Scheme 1), we reasoned that the pentacyclic structure could be constructed from an eight-membered *N*-hydroxybenzazocinone intermediate such as **8**. For the introduction of the hydroxymethyl group, we planned to perform a stereoselective hydroxymethylation using a steric bias created by the protected 1,2-diol moiety. The eight-membered ring would be formed by an intramolecular Mitsunobu reaction[18] of the ω-hydroxynitrobenzenesulfonamide (Ns-amide).[19] The cyclization precursor **9** would be assembled from an aromatic fragment **11** and the chiral side-chain unit **12**, which would be derived easily from tartaric acid.

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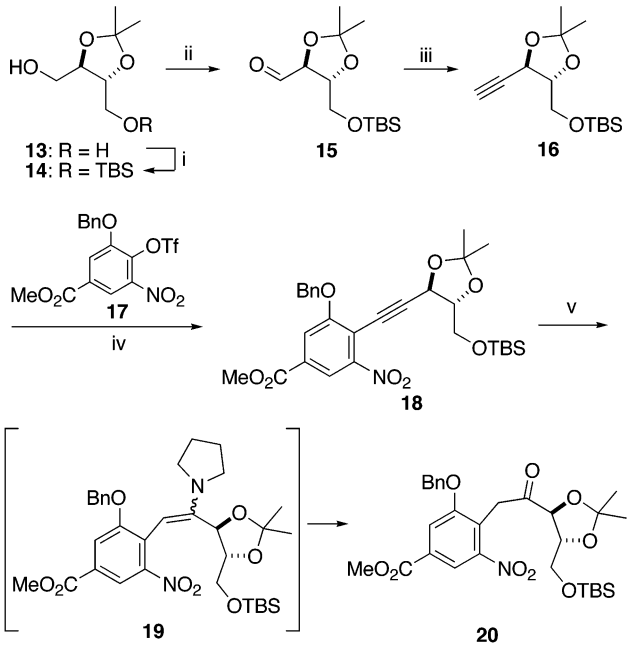
SCHEME 4. Synthesis of Ketone 20[a]

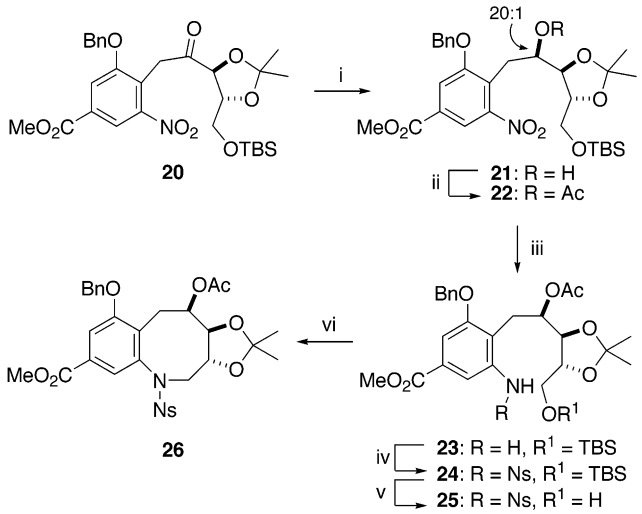


[a] Reagents and conditions: (i) NaH, TBSCl, THF, 0 °C, 1.5 h, 76%; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N, −78 °C to rt; (iii) dimethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3, MeOH, 0 °C to rt, 2 h, 49% (2 steps); (iv) $Pd(OAc)_2$ (10 mol %), Ph_3P (20 mol %), THF/ Et_3N (2/1), 65 °C, 2 h, 83%; (v) pyrrolidine, benzene, rt, 1 h, then 50% aq AcOH, rt, 4 h, 90%.

2. Synthesis of the Cyclization Precursor via a Novel Ketone Formation Reaction. The synthesis began with the preparation of the arylacetylene **18** (Scheme 4). Monosilylation of 2,3-di-*O*-isopropylidene-D-threitol (**13**),[20] which is readily available from D-tartaric acid, gave the silyl ether **14**. After Swern oxidation,[21] the resultant aldehyde **15** was treated with dimethyl 1-diazo-2-oxopropylphosphonate in the presence of K_2CO_3, which led to the terminal acetylene **16**.[22,23] However, the Sonogashira coupling[24] reaction of **16** with the triflate **17**[10] under standard conditions ($PdCl_2(PPh_3)_2$ and CuI in Et_3N) gave a substantial amount of the byproduct due to homocoupling of the acetylene **16**. After screening various conditions, we found that the desired cross-coupling reaction was best effected with $Pd(OAc)_2$ and Ph_3P in a mixture of THF and Et_3N at 65 °C to afford the arylacetylene **18** in 83% yield.

The next task was to convert the arylacetylene **18** into the ketone **20**. Conventional conditions such as the palladium-mediated hydration reaction usually gives a mixture of regioisomeric ketones.[25] Thus, it was necessary to devise a novel protocol to carry out this transformation regioselectively. An extensive investigation revealed that an unprecedented conjugate addition of secondary amines to the *o*-nitroarylacetylenes occurred regioselectively to generate the desired enamine. Thus, treatment of the acetylene **18** with pyrrolidine gave the corresponding enamine **19** at room temperature, which was then hydrolyzed under acidic conditions (50% $AcOH/H_2O$) to afford the ketone **20** in 90% overall yield from **18**.

SCHEME 5. Synthesis of Benzazocine 26[a]



[a] Reagents and conditions: (i) $Zn(BH_4)_2$, Et_2O, −19 °C, 2.5 h; (ii) Ac_2O, DMAP, pyridine, rt, 3 h, 92% (two steps); (iii) H_2, 5% Pt/C, MeOH, rt, 52 h, 65%; (iv) 2-NsCl, pyridine, rt, 1 h, 73%; (v) TBAF, THF, rt, 41 h; (vi) DEAD, Ph_3P, benzene, rt, 1 h, 71% (two steps).

3. First-Generation Approach to the Pentacyclic Key Intermediate. Formation of the Eight-Membered Benzazocine Ring by Ns Protocol. Having synthesized the ketone **20** in a straightforward manner, we then focused our attention on the construction of the eight-membered benzazocine ring. To this end, we examined the intramolecular Mitsunobu reaction[18] of an *ω*-hydroxynitrobenzenesulfonamide **25**, since this protocol has proved to be effective for formation of medium-sized cyclic secondary amines.[26]

The ketone **20** was reduced stereoselectively with $Zn(BH_4)_2$[27] to give the alcohol **21**, which was subjected to acetylation and removal of the minor diastereomer by column chromatography on silica gel to give **22** (Scheme 5). The nitro group was then selectively reduced by hydrogenation over Pt/C to give the aniline **23**, which was converted to the nitrobenzenesulfonamide **24** by treatment with 2-NsCl in pyridine. Finally, desilylation of **24** with TBAF provided the cyclization precursor **25**. The crucial intramolecular Mitsunobu reaction[18] took place at room temperature by slow addition of a toluene solution of DEAD to the reaction mixture to give the desired benzazocine **26** in 71% yield from **24**.

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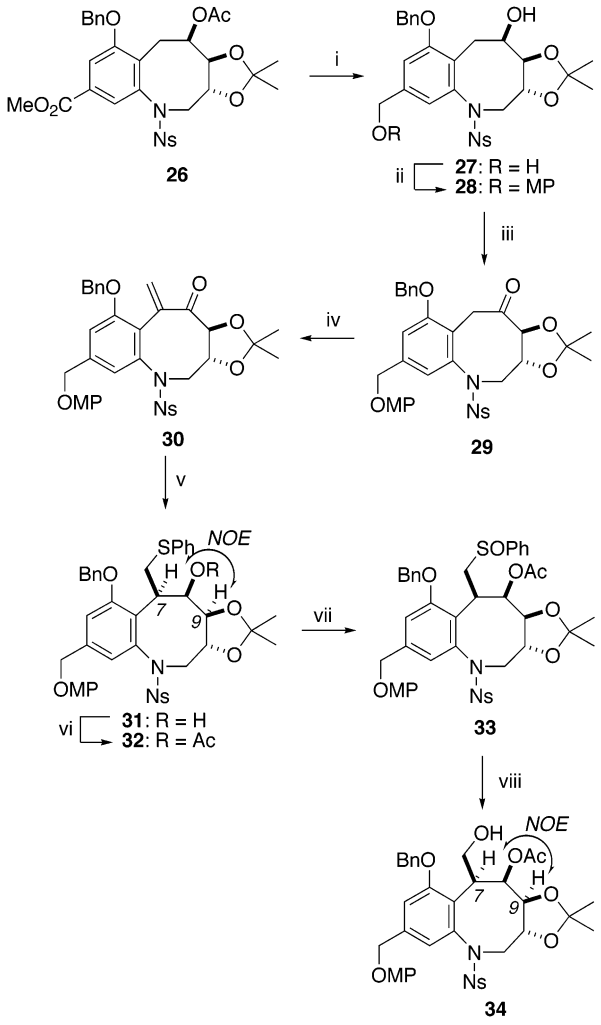
SCHEME 6. Introduction of Hydroxymethyl Group[a]



[a] Reagents and conditions: (i) DIBAL, CH_2Cl_2, −78 °C, 75 min; (ii) 4-methoxyphenol, DEAD, Ph_3P, benzene, rt, 20 min, 68% (two steps); (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 0.5 h, then Et_3N, −78 °C to rt, 72%; (iv) Me_2NH·HCl, 37% aq HCHO, Et_3N, 2-PrOH, H_2O, 90 °C, 4.5 h; (v) PhSH, Et_3N, THF, MeOH, rt, 3 h; then $NaBH_4$, 0 °C, 15 min, 84% (2 steps); (vi) Ac_2O, DMAP, pyridine, 0 °C to rt, 2.5 h, 80%; (vii) *m*-CPBA, CH_2Cl_2, −13 °C, 75 min; (viii) TFAA, Et_3N, toluene, 0 °C, 0.5 h; then $NaBH_4$, MeOH, −78 °C to rt, 1 h, 73% (two steps).

Construction of the Hydroxymethyl Group at the C(7) Position. With the eight-membered benzazocine ring in hand, we next investigated the crucial introduction of the hydroxymethyl group at the C(7) position (Scheme 6). Prior to this step, it was necessary to regenerate the ketone at the C(8) position and convert the carbomethoxy group to the *p*-methoxyphenyl ether. DIBAL reduction of the acetate **26** gave the diol **27**, whose primary alcohol was protected as the *p*-methoxyphenyl ether under Mitsunobu conditions.[18] Swern oxidation[21] of the remaining secondary alcohol furnished the ketone **29** in 72% yield. Unfortunately, hydroxymethylation (HCHO, LiOH, THF/H_2O) did not afford the desired product but instead the α,β-unsaturated ketone **30** as the major product due to elimination of the OH group.

These disappointing results prompted us to consider a stepwise conversion of the *exo*-methylene group to the hydroxymethyl group, including conjugate addition of a thiol, Pummerer reaction,[28] and reduction of the resulting aldehyde. Methylenation of the ketone **29** was best effected by treatment with Me_2NH·HCl, HCHO, and Et_3N. After Michael addition of PhSH to the α,β-unsaturated ketone **30**, the ketone functionality was reduced with $NaBH_4$ and the resulting alcohol was acetylated to give the sulfide **32** as the sole product. The sulfide **32** was oxidized with *m*-CPBA and subsequently treated with TFAA and Et_3N. Finally the reaction mixture was poured into a suspension of $NaBH_4$ in MeOH to furnish the desired primary alcohol **34** in 73% overall yield from **32**. Despite the successful installation of the hydroxymethyl group at the C(7) position, the stereochemistry of C(7), which was determined to be the *S* configuration by an NOE experiment, was opposite to that of the natural product. However, we continued our investigation since the correct stereoisomer *ent*-**34** could be prepared, in principle, using L-tartaric acid as a starting compound instead of the D-enantiomer.

Formation of the Pentacyclic Skeleton. The benzazocine derivative **34** bearing the hydroxymethyl group was next advanced to the *N*-hydroxybenzazocinone, a precursor of the hydroxylamine hemiacetal. The acetate **34** was reduced by DIBAL, and the resulting diol was monosilylated regioselectively to give the silyl ether **36**. After removal of the *o*-nitrobenzenesulfonyl group,[19] the resultant secondary amine was oxidized with *m*-CPBA to give the hydroxylamine **38**, which was protected as its acetate. Finally, Swern oxidation[21] of the secondary alcohol **39** furnished the desired ketone **40** (Scheme 7).

Upon treatment of the ketone **40** with excess hydrazine, the desired hydroxylamine hemiacetal **41** was obtained as a 79:21 mixture of the diastereomers in 78% yield. Surprisingly, however, the configuration of the C(7) stereocenter of the major product was inverted to *R*, which is same as that of the natural FR900482. The structure was confirmed by NOE experiments of the major isomer, in which a significant NOE between H(7) and H(10) was observed.

Next, the hemiacetal **41** was transformed into the pentacyclic α-epoxide **7**, the key intermediate in the synthesis of racemic FR900482 (**1**) (Scheme 8).[9] First, the four protected and unprotected hydroxyl groups were manipulated to liberate the 1,2-*trans*-diol at the 9,10-position. The acetonide **41** was converted to the tetraol **42** by heating with Amberlyst 15E in MeOH. The primary alcohol and hemiacetal were selectively protected as an acetonide to give the 1,2-diol **43**. Stereoselective construction of the α-epoxide was then executed by a four-step sequence involving silylation of the less hindered hydroxyl group at C(10), mesylation of the remaining C(9) hydroxyl group, desilylation, and finally treatment with NaH by heating in DMF to furnish the desired α-epoxide **7**, whose spectral data were identical with those of the corresponding compound reported in our racemic total synthesis.[9]

4. Second-Generation Approach to the Pentacyclic Key Intermediate. Although this newly developed synthetic route to the key epoxide **7** would formally provide **1** in optically pure form, further improvements were needed to circumvent various lengthy transforma-

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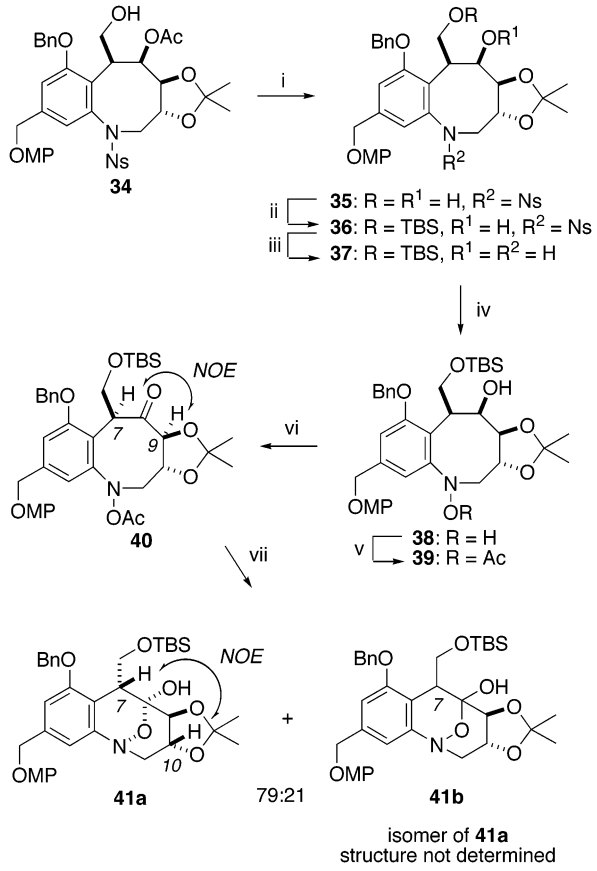
SCHEME 7. Synthesis of Hemiacetal 41[a]



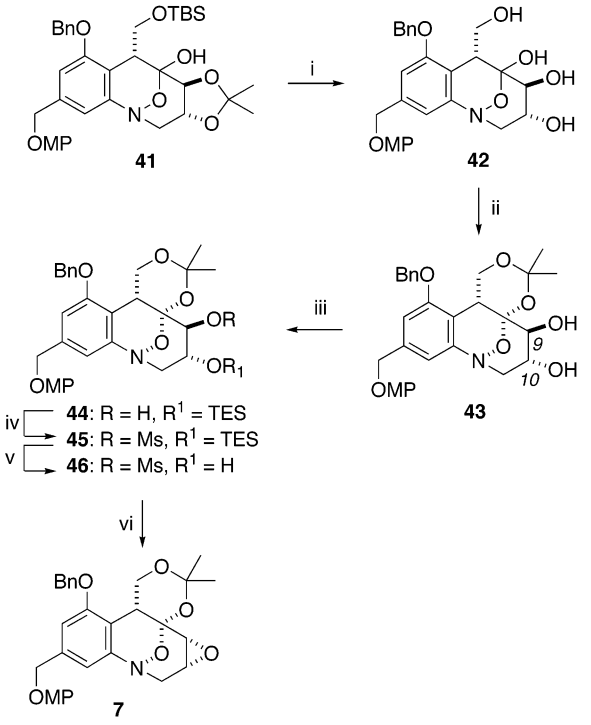
[a] Reagents and conditions: (i) DIBAL, CH_2Cl_2, −78 °C, 1 h; (ii) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 1 h; (iii) Cs_2CO_3, PhSH, MeCN, rt, 1 h, 73% (three steps); (iv) *m*-CPBA, CH_2Cl_2, rt, 30 min; (v) Ac_2O, rt, 12 h; (vi) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 0.5 h, then Et_3N, −78 °C to rt, 71% (3 steps); (vii) $NH_2NH_2 \cdot H_2O$, MeOH/CH_2Cl_2 (1/1), rt, 1 h, 78%.

tions, i.e., construction of the hydroxymethyl group and subsequent conversion to the hydroxylamine hemiacetal **41a** involving oxidation of nitrogen and protection/deprotection of hydroxyl groups. Therefore, we began reinvestigating more efficient routes.

The second-generation strategy is illustrated in Scheme 9. For construction of the eight-membered ring, we planned to exploit an intramolecular reductive cyclization of the functionalized *ω*-formyl nitrobenzene derivative **48**. We expected a direct formation of *N*-hydroxybenzazocine through selective reduction of the nitro group to the hydroxylamine[29] and subsequent intramolecular nitrone formation and reduction.[30] We also thought that, in light of the successful stereoselective hydroxymethylation of the analogous 9,10-epoxy *N*-acetyl substrate in the racemic synthesis,[31] the problematic hydroxymethylation of the C(7) position could be carried out using a 9,10-epoxy substrate.

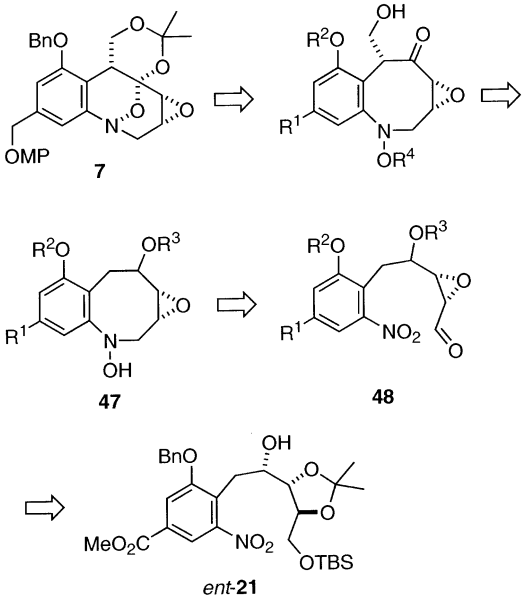
Construction of the Eight-Membered Ring by Reductive Hydroxylamination. The second-generation synthesis commenced with the stereoselective construction of the epoxide on the side chain of the cyclization precursor. The secondary alcohol in *ent*-**21**, which was prepared according to the sequence shown in Schemes 4 and 5,[32] was protected as the TIPS ether and subsequent selective removal of both the acetonide and TBS

SCHEME 8. Synthesis of the Key Intermediate 7[a]



[a] Reagents and conditions: (i) Amberlyst 15E, MeOH, 40 °C, 1 h, 90%; (ii) PPTS, 2-methoxypropene, 2,2-dimethoxypropane, acetone, rt, 40 min, 78%; (iii) TESCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 3 h; (iv) MsCl, Et_3N, CH_2Cl_2, rt, 3 h; (v) TBAF, THF, rt, 1 h, 80% (3 steps); (vi) NaH, DMF, 120 °C, 10 min, 90%.

SCHEME 9. Second-Generation Strategy

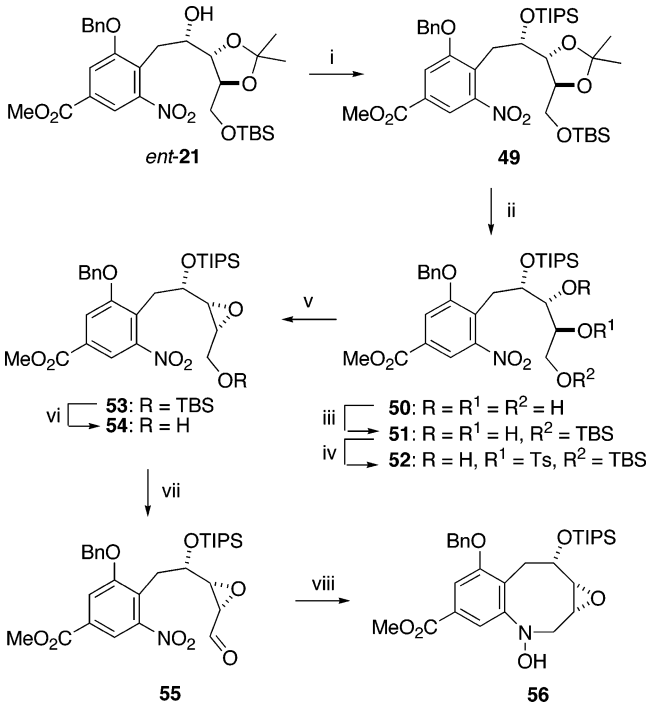


(29) For examples, see; (a) Kamm, O. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 445. (b) Davey, M. H.; Lee, V. Y.; Miller, R. D.; Marks, T. J. *J. Org. Chem.* **1999**, *64*, 4976. (c) Wood, W. W.; Kremp, G.; Petry, T.; Simon, W. E. J. *Synth. Commun.* **1999**, *29*, 619.

(30) For a synthetic approach based on a similar concept, see; ref 8a.

(31) In the synthesis of racemic FR900482, we succeeded in obtaining stereoselective installation of the side chain at the C(7) position by using an *N*-acetyl-9,10-epoxybenzazocinone derivative; see ref 9.

SCHEME 10. Synthesis of *N*-Hydroxybenzazocine 56[a]



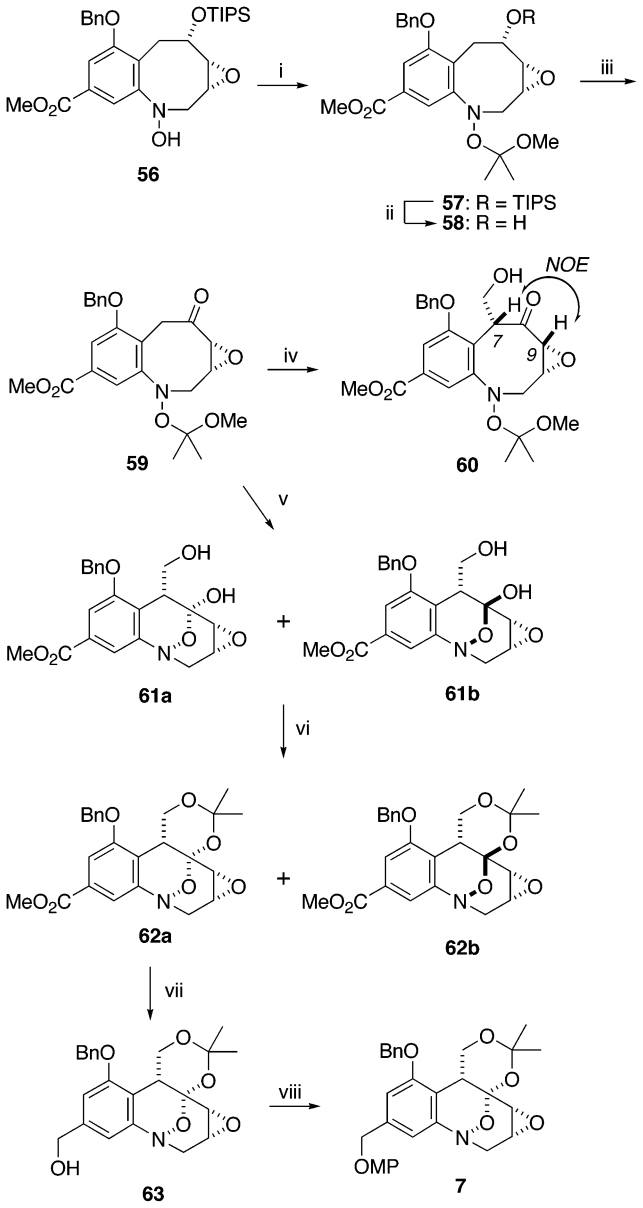
[a] Reagents and conditions: (i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 7 h; (ii) AcOH/H_2O (5/1), 100 °C, 4 h, 61% (two steps); (iii) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 13 h; (iv) TsCl, DABCO, CH_2Cl_2, rt, 1.5 h; (v) NaH, DMF, 0 °C to rt, 1 h, 76% (3 steps); (vi) CSA, MeOH, rt, 1 h; (vii) Dess−Martin periodinane, CH_2Cl_2, 0 °C to rt, 0.5 h; (viii) H_2, 5% Pt/C, MeOH, rt, 2 h, 89% (three steps).

group by heating in a mixture of AcOH and H_2O furnished the triol **50** (Scheme 10). The triol **50** was converted to the desired α-epoxide **53** by selective protection of the primary alcohol, regioselective tosylation of the sterically less hindered hydroxyl group, and finally treatment with NaH to furnish the α-epoxide **53** in 76% overall yield from **50**.

With the epoxide in hand, we focused our attention on the reductive cyclization of the eight-membered ring. Conversion of the TBS ether **53** to the cyclization precursor **55** was performed by desilylation followed by oxidation of the resulting primary alcohol with Dess−Martin periodinane.[33] After screening several catalysts (Pt/C, PtO_2, Rh/C) and solvents (MeOH, THF, AcOEt), we found that catalytic hydrogenation over Pt/C in MeOH cleanly proceeded to give the *N*-hydroxybenzazocine **56** as the sole product in 89% overall yield from **53**. No product due to overreduction was observed.

Stereoselective Hydroxymethylation and Facile Construction of the Pentacyclic Hydroxylamine Hemiacetal Structure. Having successfully constructed the *N*-hydroxybenzazocine ring, we were ready for the key construction of the hydroxymethyl group at the C(7) position. The hydroxylamine was protected as the 1-methoxy-1-methylethyl ether and then the TIPS group was removed. The liberated secondary alcohol **58** was subjected to Swern oxidation[21] to afford the ketone **59**

SCHEME 11. Synthesis of the Pentacyclic Intermediate 7[a]



[a] Reagents and conditions: (i) 2-methoxypropene, TsOH·H_2O, CH_2Cl_2, rt, 10 min; (ii) TBAF, THF, rt, 12 h, 91% (two steps); (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 0.5 h, then Et_3N, −78 °C to rt, 0.5 h, 82%; (iv) 37% aq HCHO, LiOH, THF/H_2O (20/3), 0 °C, 5 h, 52%, 94:6; (v) 37% aq HCHO, LiOH, THF/H_2O (20/3), 0 °C, 5 h; then 1 N HCl, 0 °C to rt, 10 h, **61a**/**61b** = 87:13; (vi) PPTS, 2-methoxypropene, 2,2-dimethoxypropane, acetone, rt, 3 h, 65% (from **59**); (vii) DIBAL, CH_2Cl_2, −78 °C, 1 h, 99%; (vii) 4-methoxyphenol, DEAD, Ph_3P, benzene, rt, 15 min, 96%.

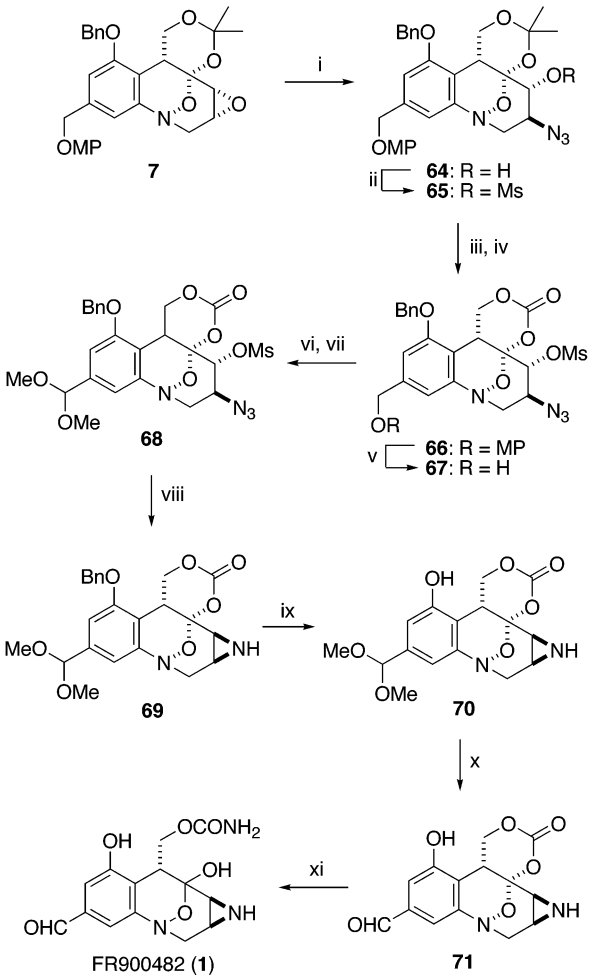
(Scheme 11). The crucial hydroxymethylation was best effected by treatment of the ketone **59** with a catalytic amount of LiOH and excess formalin in aqueous THF at 0 °C to furnish the desired 7-hydroxymethyl benzazocinone **60** with high diastereoselectivity (94:6). The stereochemistry of the major isomer was unambiguously established to be the required C(7) *R* based on the NOE observation between H(7) and H(9).

In practice, we performed a more efficient one-pot conversion of the ketone **59** into the hydroxylamine hemiacetals. Thus, after hydroxymethylation, the reac-

(32) For a detailed experimental procedure, see the Supporting Information.

(33) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

SCHEME 12. Total Synthesis of FR900482 (1)[a]



[a] Reagents and conditions: (i) LiN_3, DMF/H_2O (10/1), 120 °C, 3.5 h, 83%; (ii) MsCl, Et_3N, CH_2Cl_2, rt, 3 h, 80%; (iii) TFA, CH_2Cl_2, rt, 3 h; (iv) $(Cl_3CO)_2C{=}O$, pyridine, CH_2Cl_2, 0°C, 30 min, 92% (two steps); (v) $(NH_4)_2Ce(NO_3)_6$, MeCN/H_2O (4/1), rt, 10 min, 84%; (vi) PCC, $MgSO_4$, CH_2Cl_2, rt, 1.5 h; (vii) CSA, $CH(OMe)_3$/MeOH (1/4), rt, 1 h, 81% (two steps); (viii) Ph_3P, *i*-Pr_2NEt, THF/H_2O (10/1), 60 °C, 1.5 h, 85%; (ix) H_2 (1 atm), 10% Pd/C, EtOH, rt, 2.5 h, 97%; (x) 1% $HClO_4$, THF/H_2O (10/1), rt, 3.5 h; (xi) NH_3 (gas), THF, rt, 2 h, 83% (two steps).

tion mixture was acidified with 1 N HCl to remove the mixed-acetal protecting group on the hydroxylamine. The reaction was allowed to warm to room temperature, and the desired hemiacetal was obtained as a mixture of the diastereomeric tautomers (**61a**/**61b** 87:13). This mixture was then subjected to acetonide formation to give the pentacyclic epoxide **62a** (56% isolated yield from the ketone **59**). Finally, DIBAL reduction of methyl ester and protection of the resulting benzyl alcohol as the *p*-methoxyphenyl ether[34] gave the pentacyclic intermediate **7**, a key intermediate for the synthesis of FR900482 (**1**).

5. Completion of the Total Synthesis. Finally, the total synthesis of optically pure FR900482 (**1**) was completed by a modification of our racemic synthesis (Scheme 12).[9] Regioselective ring-opening of the epoxide **7** took place with LiN_3 in aqueous DMF at 120 °C. After mesylation of the hydroxyl group, the acetonide was converted to the cyclic carbonate **66** by hydrolysis with TFA and treatment with triphosgene in the presence of pyridine. The *p*-methoxyphenyl group was removed by treatment with ceric ammonium nitrate,[34] and the resulting alcohol was oxidized with PCC to afford the corresponding benzaldehyde derivative. The relatively unstable formyl group was protected as the dimethyl acetal **68**. Next, aziridine **69** was prepared by heating the mesylate **68** with Ph_3P in aqueous THF in the presence of *i*-Pr_2NEt. Removal of the two protective groups, the benzyl ether and the dimethyl acetal, was successfully carried out by standard hydrogenation and cautious addition of 1% $HClO_4$ in aqueous THF, respectively. Finally, regioselective ammonolysis was executed by bubbling ammonia gas into a THF solution of the carbonate **71** to give FR900482. The synthetic material was identical with an authentic sample in all respects.[1b,2a]

6. Stereochemical Issues in Hydroxymethylation and Hydroxylamine Hemiacetal Formation. Controlling the stereochemistry in the hydroxymethylation at the C(7) position and the hydroxylamine hemiacetal formation was a critical aspect in both routes described herein and merits more detailed discussions.

In the first generation synthesis, the stepwise sequence for the construction of the hydroxymethyl group at the C(7) position provided the C(7) *S* isomer **34** although the C(7) *R* isomer was required for the synthesis of the natural FR900482 (Scheme 6). This is probably due to a protonation from the less-hindered α-face in the conjugate addition of thiophenol to the enone **30**. However, after the formation of the hydroxylamine hemiacetal, the configuration of the C(7) chiral center of the major product **41a** was determined to be C(7) *R* (Scheme 7). This observation could be explained by the fact that during the formation of the hydroxylamine hemiacetal, epimerization of the C(7) chiral center took place due to enolization of the *N*-hydroxybenzazocinone derivative **40** with excess hydrazine, resulting in the formation of the thermodynamically most stable isomer as the major product.[35] In fact, when the ketone **40** was treated with excess hydrazine in a mixture of CD_3OD-$CDCl_3$, the C(7) position of the resulting hemiacetal was completely deuterated, suggesting a facile enolization of the ketone **40** under weakly basic conditions. In addition, the thermal stability of the major isomer is supported by preliminary semiempirical calculations comparing the relative stability of all four possible isomers of the model compounds (**72**−**75**, Figure 1).[36] As shown in Figure 1, the 7α-isomers (**72**, **73**) are lower in energy relative to the corresponding 7*β*-isomers (**74**, **75**).

In the second-generation synthesis, the C(7) *R* stereochemistry could be successfully established by an aldol reaction, in which hydroxymethylation of the lithium enolate occurred from the less hindered α-side (Scheme 11). In contrast to the formation of the hydroxylamine hemiacetal under the weakly basic conditions discussed above, the ketone **60** was successfully converted to the hemiacetals **61a** and **61b** with retention of the C(7) configuration under mildly acidic conditions (Scheme 13).

(34) Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291.

(35) For formation of a hydroxylamine hemiacetal derivative possessing the same relative stereochemistry corresponding to C(7), C(9), and C(10), see ref 16.

(36) The minimizations were performed on the simplified models using the SPARTAN program (SPARTAN '02, ver 1.0) employing PM3 parameters.

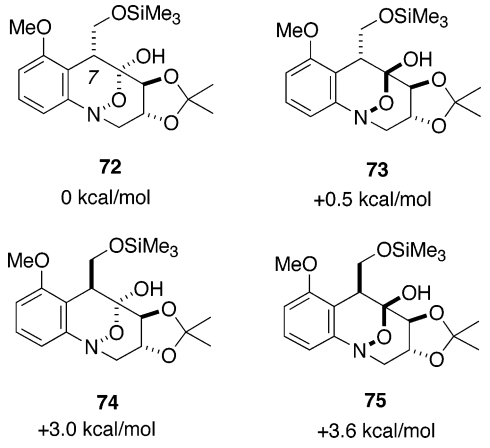
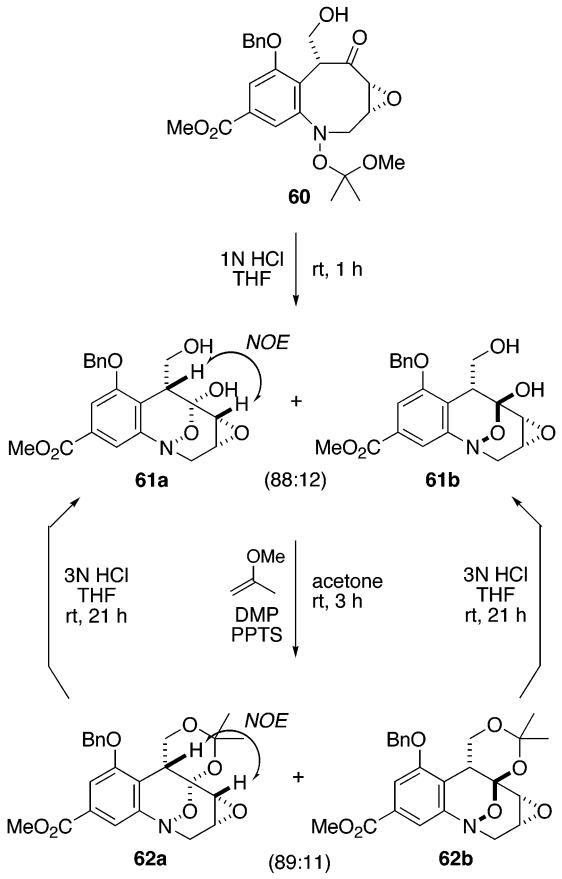


FIGURE 1. Relative energies of the four diastereoisomeric hemiacetals.

SCHEME 13



In addition, subjection of the mixture of **61a** and **61b** to acidic acetalization conditions provided the corresponding mixture of acetonides **62a** and **62b** in the same ratio as **61a**/**61b**. Furthermore, removal of the acetonide from the separated **62a** or **62b** gave the corresponding hemiacetal **61a** or **61b**, respectively, as the exclusive product with no appreciable formation of the other isomers. Therefore, it is likely that under acidic conditions, the formation of the hydroxylamine hemiacetal would be a kinetically controlled process and once the hemiacetal is formed, no interconversion of the diastereomeric hemiacetals **61a** and **61b** by ring opening back to the keto-form **60** would take place.[37]

Conclusion

We have accomplished an enantioselective total synthesis of the antitumor antibiotic FR900482 (**1**).[38] The precursor for the cyclization of the benzazocine ring could be prepared effectively by taking advantage of the newly developed ketone formation from the *o*-nitrophenylacetylene derivatives. For the formation of the eight-membered benzazocine ring, we devised two different methods, namely, a nitrobenzenesulfonamide protocol and an intramolecular reductive hydroxylamination reaction. These methods should be useful not only for this class of compounds but also for a range of medium-sized nitrogen-containing cyclic compounds. The critical stereoselective construction of the hydroxymethyl side chain at the C(7) position and the hydroxylamine hemiacetal could be performed by a facile one-pot protocol that enabled us to synthesize the pentacyclic key intermediate **7**.

Experimental Section

[(4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (14). To a suspension of NaH (60% in oil, 30.0 g, 1.25 mol) in THF (1 L) was added a solution of 2,3-di-*O*-isopropylidene-D-threitol (**13**) (87.5 g, 0.54 mol) in THF (150 mL) dropwise over 1 h at room temperature. The reaction mixture was stirred for an additional 1 h and cooled to 0 °C. To the mixture was added a solution of TBSCl (97.6 g, 0.65 mol) in THF (200 mL) dropwise over 1 h. Stirring was continued for 30 min, and the reaction mixture was poured into crushed ice (300 mL) and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (hexane/EtOAc, 9:1 then 1:1) on silica gel to afford **14** (113 g, 76%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (td, J = 4.6, 7.6 Hz, 1H), 3.91−3.86 (m, 2H), 3.79−3.64 (m, 3H), 2.38 (dd, J = 4.4, 8.3 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.1, 80.2, 78.1, 63.7, 62.7, 27.0, 26.9, 25.8, 18.3, −5.52, −5.55; IR (neat) 3466, 1254, 1083 cm^{-1}; $[\alpha]^{23}_D$ −13.8 (*c* 1.09, $CHCl_3$); MS (ESI) *m*/*z* 277 ([M + H]$^+$).

[(4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyne (16). To a solution of oxalyl chloride (36.8 g, 0.29 mol) in CH_2Cl_2 (1 L) was added a solution of DMSO (34.1 mL, 0.48 mol) in CH_2Cl_2 (50 mL) at −78 °C, and the resulting solution was stirred for 10 min. A solution of the alcohol **14** (67.3 g, 0.24 mol) in CH_2Cl_2 (70 mL) was added dropwise over 30 min. After the solution had stirred for an additional 30 min, Et_3N (100 mL, 0.72 mol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was poured into 10% aqueous citric acid and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude aldehyde **15** (57.3 g) as a pale yellow oil. The crude aldehyde was dissolved in MeOH (1 L), to which was added K_2CO_3 (58.0 g, 0.42 mol) then dimethyl 1-diazo-2-oxopropylphosphonate (48.4 g, 0.25 mol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was filtered through a pad of Celite, and concentrated. The residue was taken up in EtOAc and the

(37) The C(7) position of the tetraol **42** was not deuterated by treatment with trifluoroacetic acid-*d*, suggesting no enolization under acidic conditions.

(38) To compare the efficiency of the first and the second generation syntheses, total number of steps and total yields from the commercially available 2,3-di-*O*-isopropylidenethreitol were calculated. Total yield of **1** was ca. 0.12% over 43 total steps by the first-generation synthesis and ca. 2.1% over 32 steps by the second-generation synthesis.

solution was washed with brine, dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash column chromatography (hexane/EtOAc, 9:1 then 1:1) on silica gel to afford **16** (31.6 g, 49%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (dd, J = 2.2, 7.3 Hz, 1H), 4.12 (td, J = 4.2, 7.3 Hz, 1H), 3.78 (d, J = 4.2 Hz, 2H), 2.51 (d, J = 2.2 Hz, 1H), 1.49 (s, 3H), 1.41 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.6, 82.1, 81.2, 74.3, 66.9, 61.9, 26.8, 26.2, 25.8, 18.3, −5.37, −5.48; IR (neat) 3313, 1255, 1087 cm^{-1}; $[\alpha]^{23}_D$ +11.8 (*c* 0.92, $CHCl_3$); MS (EI) *m*/*z* 270 ([M]$^+$).

Methyl 3-Benzyloxy-4-[(4*R*,5*R*)-5-(*tert*-butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]ethynyl-5-nitrobenzoate (18). To a mixture of the triflate **17** (39.2 g, 88.7 mmol), Ph_3P (4.65 g, 17.7 mmol), and $Pd(OAc)_2$ (1.99 g, 8.87 mmol) in degassed THF/ Et_3N (200 mL/200 mL) under Ar was added a solution of the acetylene **16** (27.5 g, 0.129 mol) in THF (200 mL) dropwise over 1.5 h at 65 °C. The reaction mixture was stirred for 30 min at the same temperature. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and 10% aqueous citric acid. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated, and purified by flash column chromatography (hexane/EtOAc, 9:1) on silica gel to afford **18** (40.9 g, 83%) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 1.4 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.49−7.33 (m, 5H), 5.24 (s, 2H), 4.92 (d, J = 7.0 Hz, 1H), 4.23 (ddd, J = 3.6, 3.9, 7.0 Hz, 1H), 3.96 (s, 3H), 3.79 (dd, J = 3.9, 11.2 Hz, 1H), 3.74 (dd, J = 3.6, 11.2 Hz, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 0.89 (s, 9H), 0.070 (s, 3H), 0.067 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 160.7, 151.1, 135.2, 130.7, 128.7, 128.4, 127.2, 117.4, 116.2, 112.0, 110.9, 102.6, 82.2, 76.3, 71.4, 67.4, 61.8, 52.9, 26.8, 25.9, 25.8, 18.3, −5.36, −5.49; IR (neat) 1731, 1539, 1297, 1245, 1056 cm^{-1}; $[\alpha]^{23}_D$ +38.8 (*c* 0.70, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{41}N_2O_8Si$ ([M + NH_4]$^+$) 573.2632, found 573.2695.

Methyl 3-Benzyloxy-4-[2-[(4*S*,5*R*)-5-(*tert*-butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo]-ethyl-5-nitrobenzoate (20). To a solution of the alkyne **18** (11.5 g, 20.7 mmol) in benzene (60 mL) was added pyrrolidine (6.00 mL, 72.5 mmol), and the mixture was stirred for 1 h at room temperature. To the mixture was added 50% aqueous acetic acid (40 mL), and the resulting mixture was vigorously stirred for 4 h at room temperature. The separated organic layer was washed with saturated aqueous $NaHCO_3$, 10% aqueous citric acid, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 50:1 then 10:1) on silica gel to afford **20** (10.7 g, 90%) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 1.5 Hz, 1H), 7.85 (d, J = 1.2 Hz, 1H), 7.41−7.34 (m, 5H), 5.15 (s, 2H), 4.52 (d, J = 18.6 Hz, 1H), 4.45 (d, J = 7.8 Hz, 1H), 4.40 (d, J = 18.6 Hz, 1H), 4.08 (ddd, J = 3.0, 3.6, 7.8 Hz, 1H), 3.96 (s, 3H), 3.85 (dd, J = 3.0, 11.5 Hz, 1H), 3.68 (dd, J = 3.6, 11.5 Hz, 1H), 1.46 (s, 3H), 1.37 (s, 3H), 0.89 (s, 9H), 0.062 (s, 3H), 0.058 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 165.3, 158.0, 150.6, 135.5, 130.9, 129.1, 128.9, 128.0, 124.6, 118.4, 116.6, 111.2, 81.1, 79.1, 71.9, 62.8, 53.1, 37.7, 27.2, 26.5, 26.2, 18.7, −4.98, −5.15; IR (neat) 1731, 1538, 1292 cm^{-1}; $[\alpha]^{23}_D$ −12.5 (*c* 0.56, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{40}NO_9Si$ ([M + H]$^+$) 574.2472, found 574.2485.

Methyl 3-Benzyloxy-4-[(2*S*)-2-[(4*R*,5*S*)-5-(*tert*-butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-triisopropylsilyloxy]ethyl-5-nitrobenzoate (49). To a solution of the secondary alcohol *ent*-**21** (12.5 g, 21.7 mmol) in CH_2Cl_2 (60 mL) was added 2,6-lutidine (15.1 mL, 130 mmol) followed by TIPSOTf (17.5 mL, 65.1 mmol) at 0 °C. After being stirred at room temperature for 7 h, the reaction mixture was diluted with $CHCl_3$ and washed with saturated aqueous $NaHCO_3$ and brine. The separated organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude TIPS ether **49** (22.7 g), which was used for the next reaction without further purification. A small portion of the crude product was purified by preparative TLC (hexane/EtOAc 4:1) to give the pure **49** as a yellow oil for the characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 1.5 Hz, 1H), 7.76 (d, J = 1.5 Hz, 1H), 7.44−7.36 (m, 5H), 5.16 (d, J = 11.2 Hz, 1H), 5.12 (d, J = 11.2 Hz, 1H), 4.31−4.26 (m, 1H), 4.03−3.99 (m, 1H), 3.95 (s, 3H), 3.64 (dd, J = 4.4, 11.2 Hz, 1H), 3.60 (dd, J = 3.9, 11.2 Hz, 1H), 3.56 (dd, J = 3.9, 7.8 Hz, 1H), 3.48 (dd, J = 7.3, 12.7 Hz, 1H), 3.33 (dd, J = 7.8, 12.7 Hz, 1H), 1.31 (s, 3H), 1.25 (s, 3H), 0.98−0.90 (m, 21H), 0.80 (s, 9H), −0.026 (s, 3H), −0.029 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 158.0, 152.1, 135.3, 129.6, 128.7, 128.6, 128.0, 127.3, 117.9, 114.9, 108.9, 79.6, 77.1, 71.4, 70.6, 63.5, 52.7, 30.5, 26.9, 26.7, 25.8, 18.2, 18.1, 12.9, −5.48, −5.57; IR (neat) 2947, 1730, 1540, 1289, 1140 cm^{-1}; $[\alpha]^{23}_D$ +23.4 (*c* 1.26, $CHCl_3$); MS (ESI) *m*/*z* 732 ([M + H]$^+$).

Methyl 3-Benzyloxy-5-nitro-4-[(2*S*,3*R*,4*S*)-3,4,5-trihydroxy-2-triisopropylsilyloxypentyl]benzoate (50). A solution of the preceding TIPS ether **49** (10.1 g) in AcOH/H_2O (100 mL/20 mL) was heated at 100 °C for 4 h. The solvent was removed under reduced pressure, and the resulting residue was purified by flash column chromatography (hexane/EtOAc, 9:1 then 1:1) on silica gel to afford **50** (3.37 g, 61% from *ent*-**21**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 1.5 Hz, 1H), 7.79 (d, J = 1.0 Hz, 1H), 7.46−7.36 (m, 5H), 5.18 (s, 2H), 4.46−4.41 (m, 1H), 3.94 (s, 3H), 3.60−3.54 (m, 2H), 3.48−3.39 (m, 2H), 3.27 (dd, J = 6.4, 13.2 Hz, 1H), 3.17−3.13 (m, 1H), 2.99 (br, 1H), 2.68 (d, J = 7.8 Hz, 1H), 2.18 (br, 1H), 0.87−0.96 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 157.8, 151.9, 135.1, 130.2, 128.8, 128.7, 128.2, 125.7, 117.71, 117.65, 115.3, 115.2, 72.1, 71.70, 71.66, 71.5, 63.9, 52.7, 30.8, 18.0, 12.7; IR (neat) 3447, 1725, 1535, 1291 cm^{-1}; $[\alpha]^{23}_D$ +30.9 (*c* 1.35, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{44}NO_9Si$ ([M + H]$^+$) 578.2785, found 578.2820.

Methyl 3-Benzyloxy-4-[(2*S*,3*R*,4*S*)-5-(*tert*-butyldimethylsilyloxy)-3,4-dihydroxy-2-triisopropylsilyloxy]pentyl-5-nitrobenzoate (51). To a solution of the triol **50** (3.36 g, 5.82 mmol) in CH_2Cl_2 (15 mL) were successively added Et_3N (1.95 mL, 14.0 mmol), DMAP (73 mg, 0.60 mmol), and TBSCl (1.06 g, 7.00 mmol) at room temperature. The reaction mixture was stirred for 13 h at the same temperature, diluted with $CHCl_3$, and washed with 10% aqueous citric acid, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the TBS ether **51** (4.50 g), which was used for the next reaction without further purification. A small portion of the crude product was purified by preparative TLC (hexane/EtOAc, 4:1) to give the pure **51** as a yellow oil for the characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.74 (s, 1H), 7.43−7.33 (m, 5H), 5.14 (s, 2H), 4.41−4.36 (m, 1H), 3.91 (s, 3H), 3.71−3.66 (m, 1H), 3.60−3.44 (m, 3H), 3.29 (dd, J = 7.3, 13.2 Hz, 1H), 3.24−3.20 (m, 1H), 2.82 (d, J = 2.9 Hz, 1H), 2.57 (d, J = 7.3 Hz, 1H), 0.94−0.82 (m, 21H), 0.77 (s, 9H), −0.03 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 157.9, 152.1, 135.2, 129.8, 128.8, 128.6, 127.9, 126.9, 117.8, 115.1, 73.1, 71.5, 71.3, 71.1, 64.5, 52.7, 30.0, 25.8, 18.1, 18.0, 17.9, 12.8, −5.6; IR (neat) 3545, 1730, 1539, 1290 cm^{-1}; $[\alpha]^{25}_D$ +31.3 (*c* 0.96, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{35}H_{58}NO_9Si_2$ ([M + H]$^+$) 692.3650, found 692.3624.

Methyl 3-Benzyloxy-4-[(2*S*,3*R*,4*S*)-5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-4-(toluene-4-sulfonyl)oxy-2-triisopropylsilyloxy]pentyl-5-nitrobenzoate (52). To a solution of the preceding TBS ether **51** (4.43 g) in CH_2Cl_2 (15 mL) was added DABCO (1.23 g, 11.0 mmol) followed by TsCl (1.34 mg, 7.00 mmol) at room temperature. The reaction mixture was stirred for 1.5 h and was partitioned between $CHCl_3$ and 1 N HCl. The separated organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude **52** (5.15 g), which was used for the next reaction without further purification. A small portion of the crude product was purified by preparative TLC (benzene/EtOAc, 20:1) to give the pure **52** as a yellow oil for the characterization: ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.98 (d, J = 1.5 Hz, 1H), 7.77−7.74 (m, 3H), 7.46−7.36 (m, 5H), 7.26 (d, J = 7.3 Hz, 1H), 5.20 (d, J = 11.2 Hz, 1H), 5.14 (d, J = 11.2 Hz, 1H), 4.46−4.39 (m, 2H), 3.94 (s, 3H), 3.90 (dd, J = 2.4, 12.2 Hz, 1H), 3.68 (dd, J = 3.4, 12.2 Hz, 1H), 3.54 (dd, J = 9.8, 12.7 Hz, 1H), 3.39 (t, J = 7.3 Hz, 1H), 3.18 (dd, J = 5.4, 12.7 Hz, 1H), 2.41 (s, 3H), 2.11 (d, J = 8.3 Hz, 1H), 1.00−0.87 (m, 21H), 0.67 (s, 9H), −0.08 (s, 3H), −0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 157.8, 151.9, 144.4, 135.1, 133.9, 130.1, 129.5, 128.8, 128.6, 128.2, 128.1, 125.3, 117.73, 117.69, 115.61, 115.57, 83.9, 71.68, 71.64, 70.2, 62.1, 52.7, 30.3, 25.6, 21.6, 18.08, 18.04, 13.0, −5.6, −5.7; IR (neat) 3557, 1729, 1538, 1361, 1290, 1176 cm^{-1}; $[\alpha]^{23}_D$ +17.5 (*c* 1.16, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{42}H_{67}N_2O_{11}SSi_2$ ($[M + NH_4]^+$) 863.4004, found 863.3987.

Methyl 3-Benzyloxy-4-[(2*S*)-2-[(2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxymethyl)oxiran-2-yl]-2-triisopropylsilyloxy]-ethyl-5-nitrobenzoate (53). To a solution of the tosylate **52** (4.96 g) in DMF (25 mL) was added NaH (60% in oil, 0.33 g, 8.30 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, poured into saturated aqueous NH_4Cl, and extracted with EtOAc. The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (hexane/EtOAc, 50:1 then 20:1) on silica gel to afford **53** (2.82 g, 76% from **50**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.81 (s, 1H), 7.42−7.38 (m, 5H), 5.18 (d, J = 11.7 Hz, 1H), 5.14 (d, J = 11.7 Hz, 1H), 3.98−3.94 (m, 1H), 3.94 (s, 3H), 3.29 (dd, J = 7.1, 13.2 Hz, 1H), 3.21−3.15 (m, 2H), 3.05 (dd, J = 4.4, 8.3 Hz, 1H), 2.93−2.89 (m, 1H), 2.86 (dd, J = 2.7, 11.5 Hz, 1H), 1.05−0.85 (m, 21H), 0.82 (s, 9H), −0.04 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 158.0, 151.8, 135.0, 130.2, 128.9, 128.7, 127.7, 125.7, 117.4, 115.2, 71.6, 71.0, 61.9, 60.3, 57.6, 52.7, 31.4, 25.8, 18.0, 17.9, 12.3, −5.3, −5.5; IR (neat) 1731, 1537, 1289, 1098 cm^{-1}; $[\alpha]^{25}_D$ +26.0 (*c* 1.04, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{35}H_{59}N_2O_8Si_2$ ($[M + NH_4]^+$) 691.3810, found 691.3824.

Methyl 3-Benzyloxy-4-[(2*S*)-2-[(2*R*,3*R*)-3-hydroxymethyloxiran-2-yl]-2-triisopropylsilyloxy]ethyl-5-nitrobenzoate (54). To a solution of the epoxide **53** (510 mg, 0.757 mmol) in MeOH (10 mL) was added CSA (18 mg, 76 μmol) at room temperature. After the mixture was stirred for 1 h at room temperature, saturated aqueous $NaHCO_3$ (1 mL) was added to the mixture and concentrated. The resulting residue was partitioned between EtOAc and brine. The separated organic layer was dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude **54** (427 mg), which was used for the next reaction without further purification. A small portion of the crude product was purified by preparative TLC (hexane/EtOAc, 7:3) to give the pure **54** as a yellow oil for the characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 1.5 Hz, 1H), 7.82 (s, 1H), 7.45−7.38 (m, 5H), 5.16 (d, J = 11.2 Hz, 1H), 5.12 (d, J = 11.2 Hz, 1H), 4.01 (dd, J = 7.3, 15.1 Hz, 1H), 3.96 (s, 3H), 3.33 (dd, J = 7.8, 13.2 Hz, 1H), 3.12−3.06 (m, 2H), 2.97−2.90 (m, 3H), 1.04−0.84 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 157.9, 151.9, 135.0, 130.1, 128.9, 128.4, 125.7, 117.5, 115.0, 71.7, 70.6, 61.1, 60.6, 56.8, 52.8, 31.3, 17.9, 17.8, 12.4; IR (neat) 3521, 1729, 1537, 1290 cm^{-1}; $[\alpha]^{24}_D$ −2.5 (*c* 0.87, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{42}NO_8Si$ ($[M + H]^+$) 560.2680, found 560.2655.

Methyl 3-Benzyloxy-4-[(2*S*)-2-[(2*R*,3*R*)-3-formyloxiran-2-yl]-2-triisopropylsilyloxy]ethyl-5-nitrobenzoate (55). To a solution of the primary alcohol **54** (391 mg) in CH_2Cl_2 (5 mL) was added Dess−Martin periodinane (424 mg, 1.00 mmol) at 0 °C. After being stirred at room temperature for 30 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude **55** (663 mg), which was used for the next reaction without further purification. A small portion of the crude product was purified by preparative silica gel TLC (hexane/EtOAc, 7:3) to give the pure **55** as a yellow oil for the characterization: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 5.4 Hz, 1H), 8.02 (d, J = 1.5 Hz, 1H), 7.79 (s, 1H), 7.43−7.38 (m, 5H), 5.15 (d, J = 11.2 Hz, 1H), 5.11 (d, J = 11.2 Hz, 1H), 4.27 (dd, J = 8.8, 15.1 Hz, 1H), 3.96 (s, 3H), 3.38 (dd, J = 4.9, 8.3 Hz, 1H), 3.25 (dd, J = 6.8, 13.2 Hz, 1H), 3.14−3.09 (m, 2H), 1.05−0.90 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 164.7, 157.7, 151.7, 134.8, 130.7, 128.9, 128.2, 124.3, 117.6, 115.4, 71.6, 69.6, 62.4, 58.3, 52.8, 32.0, 17.9, 17.8, 12.2; IR (neat) 1728, 1537, 1290 cm^{-1}; $[\alpha]^{24}_D$ −44.0 (*c* 1.56, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{40}NO_8Si$ ($[M + H]^+$) 558.2523, found 558.2557.

***N*-Hydroxybenzazocine (56).** A mixture of the aldehyde **55** (663 mg) and 5% Pt/C (100 mg) in MeOH (15 mL) was stirred under hydrogen atmosphere (ca. 1 atm) for 2 h at room temperature. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography ($CHCl_3$/EtOAc, 100:1 then 100:1.5) on silica gel to afford **56** (324 mg, 89% from **53**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 1.5 Hz, 1H), 7.47−7.33 (m, 6H), 5.47 (br, 1H), 5.16 (s, 2H), 4.75−4.69 (m, 1H), 3.92 (s, 3H), 3.68 (d, J = 12.7 Hz, 1H), 3.57 (dd, J = 6.1, 12.7 Hz, 1H), 3.44 (dd, J = 9.8, 16.8 Hz, 1H), 3.06 (dd, J = 6.8, 16.8 Hz, 1H), 2.88 (dd, J = 4.6, 7.6 Hz, 1H), 2.76−2.74 (m, 1H), 1.17−1.09 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 156.2, 152.9, 136.6, 129.7, 128.5, 127.9, 127.2, 127.1, 115.6, 110.2, 72.0, 70.6, 62.7, 61.6, 52.2, 50.8, 33.4, 18.0, 17.9, 12.4; IR (neat) 3424, 1722, 1301, 1104 cm^{-1}; $[\alpha]^{23}_D$ −83.4 (*c* 0.84, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{29}H_{41}NO_6Si$ ($[M]^+$) 527.2703, found 527.2713.

Secondary Alcohol (58). To a solution of the *N*-hydroxybenzazocine **56** (274 mg, 0.46 mmol) and 2-methoxypropene (1 mL, 10.4 mmol) in CH_2Cl_2 (5 mL) was added *p*-toluenesulfonic acid monohydrate (10 mg, 0.05 mmol) at room temperature. After being stirred for 10 min at room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residual material (494 mg) was dissolved in THF (5 mL), to which was added TBAF (1 M solution in THF, 1.6 mL, 1.6 mmol). After being stirred for 12 h at room temperature, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (chromatorex NH-DM2035, hexane/EtOAc, 9:1 then 7:3) to afford **58** (164 mg, 91% from **56**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.48−7.33 (m, 6H), 5.15 (d, J = 11.7 Hz, 1H), 5.11 (d, J = 11.7 Hz, 1H), 4.91−4.86 (m, 1H), 3.93 (s, 3H), 3.65−3.56 (m, 2H), 3.41 (dd, J = 9.3, 16.6 Hz, 1H), 3.12 (dd, J = 7.3, 16.6 Hz, 1H), 2.95 (s, 3H), 2.86−2.83 (m, 1H), 2.76 (brs, 1H), 2.29 (d, J = 3.6 Hz, 1H), 1.38 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 156.1, 152.8, 136.3, 129.8, 128.6, 128.1, 127.5, 117.5, 110.0, 104.2, 71.6, 70.7, 61.11, 61.07, 52.2, 51.3, 49.4, 31.0, 24.1, 23.7; IR (neat) 3439, 1720, 1212 cm^{-1}; $[\alpha]^{24}$ −27.5 (*c* 0.78, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{30}NO_7$ ($[M + H]^+$) 444.2022, found 444.2087.

Ketone (59). To a stirred solution of oxalyl chloride (44 μL, 0.50 mmol) in CH_2Cl_2 (1 mL) was added a solution of DMSO (71 μL, 1.00 mmol) in CH_2Cl_2 (0.2 mL) at −78 °C, and the mixture was stirred for 10 min. A solution of the alcohol **58** (122 mg, 0.27 mmol) in CH_2Cl_2 (1 mL) was added dropwise, and stirring continued for an additional 30 min. Et_3N (0.21 mL, 1.50 mmol) was added, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was subjected directly to flash column chromatography (chromatorex NH-DM2035, hexane/EtOAc, 9:1 then 4:1) to afford the ketone **59** (98 mg, 82%) as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6) δ 8.18 (d, J = 1.5 Hz, 1H), 7.62 (d, J = 1.0 Hz, 1H), 7.16−7.05 (m, 5H), 4.64 (d, J = 11.7 Hz, 1H), 4.60 (d, J = 11.7 Hz, 1H), 4.16 (d, J = 19.0 Hz, 1H), 3.87 (d, J = 19.0 Hz, 1H), 3.55 (s, 3H), 3.46 (d, J = 13.7 Hz, 1H), 3.28 (dd, J = 2.9, 13.7 Hz, 1H), 3.17−3.12 (m, 1H), 2.67−2.59 (m, 4H), 1.25

(s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 199.3, 166.4, 155.3, 153.3, 136.7, 130.6, 128.7, 127.0, 118.0, 110.9, 105.4, 70.5, 60.0, 58.3, 57.8, 51.8, 49.0, 40.1, 24.9, 23.1; IR (neat) 1720, 1697, 1312, 1228, 1070 cm^{-1}; $[\alpha]^{24}_D$ −22.6 (*c* 0.75, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{24}H_{27}NO_7$ 441.1788 ($[M]^+$), found 441.1836.

Three-Step Synthesis of the Hemiacetal Acetonide 62a. (1) 7-Hydroxymethylbenzazocinone (60). To a solution of the ketone **59** (75 mg, 0.17 mmol) in THF/H_2O (4 mL/0.6 mL) (20:3 v/v, 4.6 mL) were added HCHO (37% aqueous solution, 0.25 mL, 19.2 mmol) and LiOH (1 M aqueous solution, 67 μL, 67 μmol) at 0 °C. The reaction was stirred at 0 °C for 5 h and quenched by addition of 1 N NH_4Cl (67 μL, 67 μmol). The mixture was allowed to warm to room temperature, poured into brine, and extracted with EtOAc. The separated organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude 7-hydroxymethyl benzazocinones as a 94:6 mixture of diastereomers. The crude product was purified by preparative TLC (hexane/EtOAc, 1:1) to afford **60** (40 mg, 50%) and **60′** (1.2 mg, 1.5%) as colorless oils. Major isomer **60**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 1.5 Hz, 1H), 7.60 (d, *J* = 1.5 Hz, 1H), 7.48−7.33 (m, 5H), 5.25 (d, *J* = 11.2 Hz, 1H), 5.22 (d, *J* = 11.2 Hz, 1H), 4.55 (t, *J* = 9.3 Hz, 1H), 4.38 (dd, *J* = 3.4, 8.3 Hz, 1H), 3.93 (s, 3H), 3.77−3.69 (m, 1H), 3.60 (dd, *J* = 1.5, 12.7 Hz, 1H), 3.53 (dd, *J* = 4.9, 12.7 Hz, 1H), 3.42 (d, *J* = 4.9 Hz, 1H), 3.14 (br, 1H), 3.00 (dt, *J* = 1.5, 4.9 Hz, 1H), 2.55 (s, 3H), 1.34 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 166.0, 155.8, 151.4, 135.7, 128.8, 128.1, 127.4, 118.4, 111.0, 105.5, 70.9, 60.7, 60.5, 58.5, 53.3, 52.4, 49.6, 48.8, 24.6, 22.5, 14.1; IR (neat) 1719, 1580, 1292, 1232, 1212, 1070 cm^{-1}; $[\alpha]^{25}_D$ +7.8 (*c* 1.23, $CHCl_3$); MS (ESI) *m*/*z* 472 ($[M + H]^+$). Minor isomer **60′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.61 (s, 1H), 7.48−7.39 (m, 5H), 5.15 (s, 2H), 4.79 (d, *J* = 11.2 Hz, 1H), 4.36−4.30 (m, 1H), 3.95 (s, 3H), 3.92 (d, *J* = 4.9 Hz, 1H), 3.83−3.77 (m, 1H), 3.70 (d, *J* = 12.2 Hz, 1H), 3.61 (dd, *J* = 4.9, 12.2 Hz, 1H), 3.15 (t, *J* = 4.4 Hz, 1H), 2.46 (s, 3H), 1.37 (s, 3H), 1.19 (s, 3H); IR (neat) 1721, 1319, 1239, 1215 cm^{-1}.

(2) Acetonide (62a). To a solution of the 7-hydroxymethylbenzazocinone derivative **60** (14 mg, 30 μmol) in THF (1 mL) was added 1 N HCl (50 μL, 50 μmol) at room temperature. After being stirred for 1 h, the reaction mixture was poured into brine and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the hemiacetals **61a** and **61b** (12 mg, **61a**:**61b** = 88:12). To a mixture of hemiacetals **61a** and **61b** (10 mg) in acetone (0.5 mL) were added 2,2-dimethoxypropane (0.5 mL), 2-methoxypropene (12 μL, 0.13 mmol), and pyridinium *p*-toluenesulfonate (1 mg, 4 μmol) at room temperature. After being stirred for 3 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a mixture of acetonide **62a** and **62b** (**61a**/**62b** = 89:11). The crude product was purified by preparative TLC (hexane/EtOAc, 3:2) to afford the acetonides **62a** (10 mg) and **62b** (1 mg) as colorless oils. Major isomer **62a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.37(m, 5H), 7.34 (d, *J* = 1.4 Hz, 1H), 7.20 (d, *J* = 1.4 Hz, 1H), 5.17 (d, *J* = 11.7 Hz, 1H), 5.11 (d, *J* = 11.7 Hz, 1H), 4.33 (dd, *J* = 5.9, 11.7 Hz, 1H), 3.98 (d, *J* = 15.6 Hz, 1H), 3.91 (s, 3H), 3.91 (t, *J* = 10.8 Hz, 1H), 3.55 (dd, *J* = 5.4, 15.6 Hz, 1H), 3.39 (dd, *J* = 5.9, 10.8 Hz, 1H), 3.22 (t, *J* = 4.4 Hz, 1H), 3.07 (d, *J* = 4.4 Hz, 1H), 1.59 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 157.0, 147.1, 135.8, 130.6, 128.8, 128.4, 127.7, 118.4, 114.1, 107.0, 100.0, 92.9, 70.6, 59.0, 54.7, 52.4, 51.4, 49.7, 33.0, 30.0, 24.3; IR (neat) 2912, 1722, 1582, 1426, 1357, 1274, 1252, 1231, 1125, 1106, 1087, 880, 838, 778 cm^{-1}; $[\alpha]^{25}_D$ −39.9 (*c* 1.02, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{24}H_{25}NO_7$ ($[M]^+$) 439.1631, found 439.1608. Minor isomer **62b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.34 (m, 5H), 7.29 (d, *J* = 1.5 Hz, 1H), 7.12 (d, *J* = 1.0 Hz, 1H), 5.13 (d, *J* = 11.2 Hz, 1H), 5.10 (d, *J* = 11.2 Hz, 1H), 4.40 (dd, *J* = 6.3, 11.7 Hz, 1H), 3.96 (d, *J* = 15.1 Hz, 1H), 3.91 (t, *J* = 11.2 Hz, 1H), 3.89 (s, 3H), 3.72 (d, *J* = 15.1 Hz, 1H), 3.49 (d, *J* = 4.4 Hz, 1H), 3.43 (dd, *J* = 5.9, 11.2 Hz, 1H), 3.28 (d, *J* = 4.4 Hz, 1H), 1.60 (s, 3H), 1.50 (s, 3H).

Two-Step Synthesis of the Hemiacetal Acetonide 62a. (1) One-Pot Synthesis of the Hemiacetals 61a and 61b. To a solution of the ketone **59** (90 mg, 0.20 mmol) in a mixture of THF and water (20:3 v/v, 5.75 mL) was added HCHO (37% aqueous solution, 0.30 mL, 23.1 mmol) followed by LiOH (1 M aqueous solution, 80 μL, 80 μmol) at 0 °C. The reaction mixture was stirred for 5 h at 0 °C, quenched by addition of 1 N HCl (0.40 mL, 0.40 mmol), and allowed to warm to room temperature. The resulting mixture was stirred for an additional 10 h, poured into brine, and extracted with EtOAc. The separated organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product obtained was purified by preparative TLC (hexane/EtOAc, 1:1) to afford a mixture of the hemiacetals **61a** and **61b** (62 mg, 77%, **61a**/**61b** = 87:13) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.11 (m, 7H), 5.22−5.13 (m, 2H), 4.16−3.88 (m, 6H), 3.58−3.50 (m, 2H), 3.29−3.12 (m, 3H), 1.94 (br, 1H); IR (neat) 3349, 1720, 1582, 1427, 1274, 1238, 1122, 1106 cm^{-1}; $[\alpha]^{23}_D$ −16.9 (*c* 1.23, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{21}H_{21}NO_7$ ($[M]^+$) 399.1318, found 399.1371.

(2) Acetonide (62a). To a solution of a mixture of hemiacetals **61a** and **61b** (56 mg, 0.14 mmol, **61a**/**61b** = 87:13) in acetone (2.5 mL) were successively added 2,2-dimethoxypropane (2.5 mL), 2-methoxypropene (67 μL, 0.70 mmol), and pyridinium *p*-toluenesulfonate (5.0 mg, 20 μmol) at room temperature. The mixture was stirred for 3 h, and the solvent was evaporated under reduced pressure. The resulting crude product was purified by preparative TLC (hexane/EtOAc, 3:2) to afford the acetonide **62a** (51 mg, 84%) as a colorless oil.

Benzyl Alcohol (63). To a solution of the acetonide **62a** (45 mg, 0.10 mmol) in CH_2Cl_2 (3 mL) was added DIBAL (1 M solution in hexane, 0.30 mL, 0.30 mmol) at −78 °C dropwise over 5 min. The reaction mixture was stirred for 1 h, quenched by addition of MeOH (0.21 mL), and allowed to warm to room temperature. To the reaction mixture was added 30% aqueous Rochelle salt (0.36 mL), and the two-phase mixture was vigorously stirred for an additional 30 min. The mixture was poured into brine and extracted with $CHCl_3$. The separated organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by preparative TLC (hexane/EtOAc, 2:3) to afford **63** (42 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.35 (m, 5H), 6.71 (s, 1H), 6.48 (s, 1H), 5.12 (d, *J* = 11.7 Hz, 1H), 5.05 (d, *J* = 11.7 Hz, 1H), 4.62 (s, 2H), 4.31 (dd, *J* = 5.9, 11.2 Hz, 1H), 3.94 (d, *J* = 15.1 Hz, 1H), 3.89 (t, *J* = 11.2 Hz, 1H), 3.50 (dd, *J* = 4.9, 15.1 Hz, 1H), 3.35 (dd, *J* = 5.9, 11.2 Hz, 1H), 3.22 (t, *J* = 4.4 Hz, 1H), 3.06 (d, *J* = 3.9 Hz, 1H), 2.02 (br, 1H), 1.58 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 147.0, 141.9, 136.2, 128.8, 128.3, 127.5, 112.6, 110.4, 105.0, 99.9, 93.1, 70.3, 64.8, 59.3, 54.7, 51.5, 49.8, 32.6, 30.1, 24.3; IR (neat) 3482, 1584, 1432, 1119 cm^{-1}; $[\alpha]^{23}_D$ −30.3 (*c* 0.81, $CHCl_3$); HRMS (EI) *m*/*z* calcd for $C_{23}H_{25}NO_6$ ($[M]^+$) 411.1682, found 411.1721.

***p*-Methoxyphenyl Ether (7).** To a solution of the benzyl alcohol **63** (40 mg, 97 μmol) in benzene (3 mL) were successively added Ph_3P (50 mg, 0.19 mmol), *p*-methoxyphenol (24 mg, 0.19 mmol), and DEAD (40% toluene solution, 86 μL, 0.19 μmol) at room temperature. The reaction mixture was stirred for 15 min and concentrated under reduced pressure. The crude product was purified by preparative TLC (hexane/EtOAc, 3:2) to afford the *p*-methoxyphenyl ether **7** (48 mg, 96%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.35 (m, 5H), 6.89−6.77 (m, 4H), 6.74 (s, 1H), 6.54 (s, 1H), 5.12 (d, *J* = 11.4 Hz, 1H), 5.05 (d, *J* = 11.4 Hz, 1H), 4.93 (s, 2H), 4.32 (dd, *J* = 5.8, 11.5 Hz, 1H), 3.96 (d, *J* = 15.6 Hz, 1H), 3.91 (t, *J* = 11.2 Hz, 1H), 3.77 (s, 3H), 3.50 (dd, *J* = 5.1, 15.1 Hz, 1H), 3.35 (dd, *J* = 5.8, 11.0 Hz, 1H), 3.22 (t, *J* = 5.1 Hz, 1H), 3.06 (d, *J* = 3.7 Hz, 1H), 1.59 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 154.1, 152.6, 147.1, 138.3, 136.2, 128.8, 128.3, 127.5, 115.8, 114.7, 113.0, 111.2, 105.6, 99.9, 93.1,

70.3, 59.3, 55.7, 54.8, 51.5, 49.8, 32.6, 30.1, 24.3; IR (neat) 1585, 1507, 1228, 1120 cm^{-1}; $[\alpha]^{23}_D$ −24.2 (*c* 0.39, $CHCl_3$); HRMS (EI) *m/z* calcd for $C_{30}H_{31}NO_7$ ($[M]^+$) 517.2101, found 517.2145.

Hydroxyazide (64). A solution of the epoxide **7** (176 mg, 0.34 mmol) and LiN_3 (450 mg, 9.19 mmol) in DMF/H_2O (3.5 mL/0.35 mL) was heated at 120 °C for 3.5 h. The reaction mixture was cooled to room temperature, poured into crushed ice in water, and extracted with EtOAc. The separated organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 4:1) on silica gel to afford **64** (158 mg, 83%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.31 (m, 5H), 6.87−6.80 (m, 4H), 6.74 (s, 1H), 6.57 (s, 1H), 5.09 (s, 2H), 4.93 (s, 2H), 4.36 (dd, *J* = 6.1, 11.7 Hz, 1H), 4.11 (dd, *J* = 4.9, 14.2 Hz, 1H), 3.93−3.84 (m, 2H), 3.76 (s, 3H), 3.57 (dd, *J* = 3.2, 4.9 Hz, 1H), 3.32 (d, *J* = 3.3 Hz, 1H), 3.21 (dd, *J* = 6.1, 10.7 Hz, 1H), 3.18 (dd, *J* = 3.6, 13.6 Hz, 1H), 1.59 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 154.1, 152.7, 148.2, 138.4, 136.3, 128.7, 128.2, 127.5, 115.9, 114.8, 113.7, 110.6, 106.3, 100.8, 94.5, 71.9, 70.3, 59.4, 57.8, 55.7, 55.0, 33.6, 30.0, 24.3; IR (neat) 3534, 2104, 1508, 1227 cm^{-1}; $[\alpha]^{22}_D$ +58.2 (*c* 0.40, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{30}H_{33}N_4O_7$ ($[M + H]^+$) 561.2349, found 561.2383.

Mesyloxyazide (65). To a solution of hydroxyazide **64** (174 mg, 0.31 mmol) in CH_2Cl_2 (1 mL) were added Et_3N (0.14 mL, 0.98 mmol) and MsCl (0.05 mL, 0.66 mmol) at room temperature. The reaction mixture was stirred for 3 h, poured into saturated aqueous $NaHCO_3$, and extracted with EtOAc. The separated organic layer was washed with 10% aqueous citric acid and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 8:2 then 7:3) on silica gel to afford **65** (157 mg, 80%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.32 (m, 5H), 6.86−6.80 (m, 4H), 6.78 (s, 1H), 6.59 (s, 1H), 5.12 (s, 2H), 4.93 (s, 2H), 4.67 (d, *J* = 4.6 Hz, 1H), 4.39 (dd, *J* = 6.1, 10.7 Hz, 1H), 4.13 (dd, *J* = 4.6, 13.9 Hz, 1H), 4.13−4.07 (m, 1H), 3.88 (t, *J* = 10.7 Hz, 1H), 3.77 (s, 3H), 3.33 (dd, *J* = 6.1, 10.5 Hz, 1H), 3.28 (dd, *J* = 2.7, 13.9 Hz, 1H), 3.15 (s, 3H), 1.58 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 154.0, 152.6, 147.2, 138.4, 136.2, 128.6, 128.0, 127.3, 115.8, 114.6, 114.1, 110.6, 106.9, 100.4, 93.3, 78.3, 70.2, 70.1, 59.2, 57.2, 55.6, 54.4, 38.5, 33.1, 29.7, 24.3; IR (neat) 2113, 1508, 1361, 1228 cm^{-1}; $[\alpha]^{22}_D$ +45.2 (*c* 0.28, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{31}H_{35}N_4O_9S$ ($[M + H]^+$) 639.2125, found 639.2186.

Carbonate (66). To a solution of the mesyloxyazide **65** (147 mg, 0.23 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.14 mL, 1.84 mmol) at room temperature. The reaction mixture was stirred for 3 h, diluted with CH_2Cl_2, and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford a yellow residue (145 mg). To a stirred solution of triphosgene (297 mg, 1.00 mol) and pyridine (97 μL, 1.20 mmol) in CH_2Cl_2 (1 mL) was added a solution of the preceding residue (145 mg) in CH_2Cl_2 (1 mL) over a period of 10 min at 0 °C. The reaction mixture was stirred for 20 min and then partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$. The separated organic layer was washed with 10% aqueous citric acid and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting material was purified by flash column chromatography (hexane/EtOAc, 3:1) on silica gel to afford **66** (132 mg, 92% from **65**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.32 (m, 5H), 6.86−6.78 (m, 5H), 6.65 (s, 1H), 5.15 (s, 2H), 4.95 (s, 2H), 4.74−4.71 (m, 2H), 4.21 (t, *J* = 11.0 Hz, 1H), 4.17−4.11 (m, 2H), 3.75 (s, 3H), 3.64 (dd, *J* = 4.9, 11.0 Hz, 1H), 3.35 (dd, *J* = 1.5, 14.9 Hz, 1H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 154.2, 152.4, 147.0, 145.7, 140.1, 135.6, 128.9, 128.5, 127.4, 115.8, 114.7, 110.3, 109.4, 107.4, 97.0, 75.8, 70.6, 69.9, 65.7, 57.3, 55.7, 53.6, 39.1, 33.4; IR (neat) 2117, 1790, 1507 cm^{-1}; $[\alpha]^{22}_D$ +26.1 (*c* 0.30, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{29}H_{32}N_5O_{10}S$ ($[M + NH_4]^+$) 642.1870, found 642.1876.

Benzyl Alcohol (67). To a solution of the carbonate **66** (132 mg, 0.21 mmol) in MeCN/H_2O (4 mL/1 mL) and water (4:1 v/v, 5 mL) was added ammonium cerium(IV) nitrate (290 mg, 0.53 mmol) at room temperature. The reaction mixture was stirred for 10 min, poured into brine, and extracted with EtOAc. The separated organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 7:3 then 1:1) on silica gel to afford **67** (92 mg, 84%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.33 (m, 5H), 6.82 (s, 1H), 6.62 (s, 1H), 5.17 (s, 2H), 4.75−4.71 (m, 2H), 4.63 (s, 2H), 4.20 (t, *J* = 11.0 Hz, 1H), 4.17−4.08 (m, 2H), 3.64 (dd, *J* = 4.9, 11.2 Hz, 1H), 3.37 (d, *J* = 13.4 Hz, 1H), 3.30 (s, 3H), 2.21 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 146.8, 145.8, 143.5, 135.7, 128.8, 128.4, 127.3, 109.9, 109.0, 106.9, 97.0, 75.7, 70.4, 65.7, 64.4, 57.2, 53.3, 38.9, 33.2; IR (neat) 3548, 2117, 1783, 1359 cm^{-1}; $[\alpha]^{22}_D$ +38.8 (*c* 0.22, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{22}H_{26}N_5O_9S$ ($[M + NH_4]^+$) 536.1451, found 536.1464.

Dimethyl Acetal (68). To a solution of the benzyl alcohol **67** (90 mg, 0.17 mmol) in CH_2Cl_2 (3 mL) were added anhydrous $MgSO_4$ (84 mg, 0.70 mmol) and PCC (75 mg, 0.35 mmol) at room temperature. The reaction mixture was stirred for 1.5 h. Et_2O (5 mL) was added, and the mixture was stirred for an additional 30 min. The reaction mixture was passed through a pad of Celite, and the filtrate was concentrated. The resulting residue (81 mg) was dissolved in MeOH (4 mL), to which were added trimethyl orthoformate (1 mL) and CSA (3 mg, 13 μmol). The resulting mixture was stirred for 1 h at room temperature. The solution was poured into brine, and extracted with CH_2Cl_2. The separated organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 7:3) on silica gel to afford **68** (77 mg, 81% from **67**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.34 (m, 5H), 6.91 (s, 1H), 6.74 (s, 1H), 5.30 (s, 1H), 5.18 (s, 2H), 4.77−4.73 (m, 2H), 4.21 (t, *J* = 11.0 Hz, 1H), 4.16−4.12 (m, 2H), 3.64 (dd, *J* = 4.9, 11.0 Hz, 1H), 3.39 (dd, *J* = 1.2, 14.9 Hz, 1H), 3.33 (s, 3H), 3.28 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 146.6, 145.7, 140.7, 135.7, 128.8, 128.4, 127.4, 110.7, 110.2, 107.2, 101.8, 96.9, 75.8, 70.5, 65.7, 57.3, 53.3, 52.7, 52.5, 39.0, 33.4; IR (neat) 2117, 1786, 1361, 1116 cm^{-1}; $[\alpha]^{22}_D$ +18.4 (*c* 0.88, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{24}H_{30}N_5O_{10}S$ ($[M + NH_4]^+$) 580.1713, found 580.1721.

Aziridine (69). To a solution of the dimethyl acetal **68** (35 mg, 62 μmol) in THF/H_2O (1 mL/0.1 mL) were added *i*-Pr_2NEt (13 μL, 75 μmol) and Ph_3P (31 mg, 0.12 mmol). The reaction mixture was heated at 60 °C for 1.5 h and cooled to room temperature. The mixture was poured into brine and extracted with CH_2Cl_2. The separated organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (EtOAc/benzene, 1:1) to afford **69** (23 mg, 85%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.34 (m, 5H), 6.77 (s, 1H), 6.56 (s, 1H), 5.32 (s, 1H), 5.11 (s, 2H), 4.70 (dd, *J* = 5.4, 10.8 Hz, 1H), 4.25 (dd, *J* = 10.8, 11.5 Hz, 1H), 3.95 (d, *J* = 13.2 Hz, 1H), 3.67−3.62 (m, 2H), 3.31 (s, 3H), 3.29 (s, 3H), 3.00 (br, 1H), 2.43 (br, 1H), 0.54 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 149.2, 146.3, 139.5, 136.4, 128.9, 128.4, 127.5, 110.6, 109.7, 104.8, 102.5, 97.6, 70.5, 66.1, 53.0, 52.8, 52.7, 36.3, 33.6, 25.1; IR (neat) 3308, 1771, 1082 cm^{-1}; $[\alpha]^{22}_D$ +30.2 (*c* 0.45, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{23}H_{25}N_2O_7$ ($[M + H]^+$) 441.1662, found 441.1699.

Phenol (70). To a solution of the benzyl ether **69** (22 mg, 50 μmol) in EtOH (1.5 mL) was added 10% Pd/C (8 mg). The suspension was stirred at room temperature under hydrogen atmosphere (ca. 1 atm) for 2.5 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated to afford **70** (17 mg, 97%) as a colorless oil, which was used for the next reaction without further purification: ^{1}H

NMR (400 MHz, $CDCl_3$) δ 6.53 (s, 1H), 6.41 (s, 1H), 5.24 (s, 1H), 4.80 (dd, J = 5.4, 10.7 Hz, 1H), 4.23 (t, J = 11.2 Hz, 1H), 3.94 (d, J = 14.4 Hz, 1H), 3.69−3.60 (m, 2H), 3.31 (s, 3H), 3.30 (s, 3H), 3.01 (d, J = 6.6 Hz, 1H), 2.41 (d, J = 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 154.9, 148.8, 147.1, 138.6, 109.1, 107.9, 107.8, 102.7, 97.9, 65.9, 52.9, 52.7, 52.6, 35.9, 33.3, 24.7; IR (neat) 3533, 1748, 1162, 1090 cm^{-1}; MS (ESI) m/z 351 ([M + H]$^+$).

Benzaldehyde (71). To a solution of the dimethyl acetal **70** (17 mg, 49 μmol) in THF/H_2O (5 mL/0.5 mL) was added 1% perchloric acid (0.1 mL) at room temperature. The mixture was stirred for 3.5 h, poured into brine, and extracted with Et_2O. The separated organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude **71** (13 mg) as a colorless oil, which was used for the next reaction without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 6.96 (d, J = 1.5 Hz, 1H), 6.81 (d, J = 1.5 Hz, 1H), 4.83 (dd, J = 5.4, 10.8 Hz, 1H), 4.25 (t, J = 11.0 Hz, 1H), 4.01 (dd, J = 2.2, 14.6 Hz, 1H), 3.74−3.66 (m, 2H), 3.04 (d, J = 6.6 Hz, 1H), 2.47 (dd, J = 2.2, 6.6 Hz, 1H); IR (neat) 3301, 1757, 1692, 1159 cm^{-1}; MS (ESI) m/z 305 ([M + H]$^+$).

FR900482 (1). To a solution of the crude carbonate **71** (13 mg) in THF (3 mL) was bubbled ammonia gas for 15 min at room temperature. The reaction mixture was stirred for 2 h and then concentrated under reduced pressure. The crude product was purified by trituration with hexane/EtOAc to afford FR900482 (**1**) (13 mg, 83% from **70**) as a white powder: mp 165−175 °C dec; ^{1}H NMR (400 MHz, D_2O) major isomer: δ 9.76 (s, 2H), 7.08 (s, 1H), 7.06 (s, 1H), 5.13 (dd, 1H, J = 6.6, 11.5 Hz), 4.66 (dd, 1H, J = 1.2, 11.5 Hz), 3.79−3.75 (m, 2H), 3.51 (d, 1H, J = 5.1 Hz), 2.72−2.65 (m, 2H); minor isomer: δ 9.75 (s, 1H), 7.11 (d, 1H, J = 1.5 Hz), 6.96 (d, 1H, J = 1.2 Hz), 4.65 (dd, 1H, J = 5.6, 11.5 Hz), 4.44 (dd, 1H, J = 2.2, 11.5 Hz), 3.85 (dd, 1H, J = 2.4, 14.6 Hz), 3.61 (d, 1H, J = 14.9 Hz), 3.42 (dd, 1H, J = 1.9, 5.6 Hz), 2.88 (d, 1H, J = 6.8 Hz), 2.49 (dd, 1H, J = 2.4, 6.8 Hz); ^{13}C NMR (100 MHz, D_2O) major isomer: δ 197.8, 161.8, 159.0, 150.8, 138.5, 121.9, 116.5, 112.7, 96.0, 63.4, 56.1, 46.2, 32.5, 32.0; minor isomer: δ 198.0, 162.1, 157.5, 152.1, 138.4, 121.9, 115.1, 113.7, 96.2, 64.6, 55.2, 42.6, 40.3, 28.0; IR (KBr) 3287, 1692, 1587, 1347, 1087 cm^{-1}; $[\alpha]^{25}_D$ +10.0 (c 0.48, H_2O); MS (ESI) m/z 322 ([M + H]$^+$).

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Supporting Information Available: Experimental procedures and characterization data for compounds **21**−**24**, **26**, **28**−**32**, **34**−**37**, and **39**−**46**; copies of ^{1}H and ^{13}C spectra of compounds **14**, **16**, **18**, **20**−**24**, **26**, **28**−**32**, **34**−**37**, **39**−**46**, **7**, **49**−**56**, **58**−**60**, **61a**,**b**, **62a**, **63**−**70**, and **1**; ^{1}H NMR of compounds **60′**, **62b**, and **71**. This material is available free of charge via the Internet at http://pubs.acs.org.

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